REMARKS

Applicant thanks Examiner Bowman for withdrawing the rejections under 35 USC § 112 in view of the response submitted on September 18, 2009. In response to the Advisory Action mailed February 22, 2010 and the Final Office Action mailed December 10, 2009, having a period for response set to expire on March 10, 2010, Applicant respectfully requests that the Examiner favorably consider the following remarks.

Amendments to the claims

With the present submission, claim 52 has been amended, claim 53 has been canceled, and new claims 57-64 have been added. Thus, claims 52 and 54-64 are presently under consideration. Specifically, claim 52, part (a) has been amended to define the length of each strand as being between 18 and 24 nucleotides in length. Claim 52, parts (b) and (c), have been amended to recite "one or more" with respect to the modifications in the sense and antisense strand respectively with 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides. Claim 52, part (d), has been added to specify that 10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides. New claim 57 is dependent upon claim 52 and recites 10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-O-methyl nucleotides. New claim 58 is dependent upon claim 52 and recites 10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy-2'-fluoro nucleotides. New independent claim 59 recites the same features a), b), and c) as independent claim 52, but in part d) recites 10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides. New claims 60-64 are dependent upon claim 59. These amendments are supported by the instant specification as filed and detailed support is provided below.

The limitation of claims 52 and 59, part (a) *"each strand is between 18 and 24 nucleotides in length"* finds support at page 81, lines 8-10:

> *In one embodiment of the present invention, each sequence of a siRNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length.*

The limitations of claims 52 and 59, parts (b) *"the sense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand"*, (c) *"the antisense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides"*, and (d) *"10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 52) and "10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 59),* all find support at page 28, lines 12-29:

> *In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.*

The limitations of dependent claims 54, 55, 57, 58, and 60, 61, 63 and 64 all find support in the above referenced captions of the specification as filed. Support for dependent claims 56 and 62, reciting a composition comprising the siRNA molecule and a pharmaceutically acceptable carrier or diluent, can be found at page 62, lines 16-21 which reads:

In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent.

As detailed extensively in the response submitted on September 18, 2009, these combinations of features are all well exemplified throughout the specification, for example in the motifs of Table IV (please see the replacement Table IV submitted with a Preliminary Amendment dated May 19, 2009), and in numerous exemplary sequences shown in Table I and the Figures of the application as filed and the priority applications of record.

Priority

The Office declined to award the instant claims a priority that is earlier than September 5, 2002, which is the filing date of application 60/408,378. Office Action, at pages 2-3. Applicant respectfully traverses the Office's priority determination and respectfully submits that the disclosure of the priority applications relied upon not only "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter", but also contains "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same". *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985) and 35 U.S.C. § 112, ¶ 1 respectively.

The Office asserts that the passage referred to on pages 9 and 10 of application 60/358,580 does not disclose "10 or more" of each of the instant modifications, but rather discloses one or more of each. Office Action, at page 3. The Applicant respectfully traverses, as the language "one or more" represents a maximum range (*i.e.*, encompassing from one to all of the nucleotides of the strand being modified) that clearly comprises the range of "10 or more" modified nucleotides. Nevertheless, without acquiescing to the Office's position, and in the interest of advancing prosecution and putting the claims in better condition for allowance or

appeal, Applicant has amended parts (b) and (c) of claim 52 to recite "one or more" with respect to the 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications in the sense and antisense strands respectively.

Furthermore, as described in greater detail below, the amendments and instant claims are supported by all of the following priority applications: PCT/US03/05346, filed February 20, 2003; provisional application 60/408,378, filed September 5, 2002; provisional application 60/386,782, filed June 6, 2002; and provisional application 60/358,580, filed February 20, 2002.

PCT/US03/05346, filed on February 20, 2003, supports the instant claims as follows:

The limitation of claims 52 and 59, part (a) *"each strand is between 18 and 24 nucleotides in length"* finds express support at page 56, lines 4-6:

> *In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length.*

The limitations of claims 52 and 59, parts (b) *"the sense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand"*, (c) *"the antisense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides"*, and (d) *"10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 52) and "10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 59),* all find support in the paragraph bridging pages 19 and 20:

> *In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the*

antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

The present claims are also fully supported by the motifs of Table IV and in numerous exemplary sequences shown in Table I and the Figures of the PCT application.

Provisional application 60/408,378, filed September 5, 2002, supports the instant claims as follows:

The limitation of claims 52 and 59, part (a) *"each strand is between 18 and 24 nucleotides in length"* finds express support at page 38, lines 19-21:

> *In one embodiment of the present invention, each sequence of a siRNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length.*

The limitations of claims 52 and 59, parts (b) *"the sense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand"*, (c) *"the antisense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides"*, and and (d) *"10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 52) and "10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 59),* all find support in the paragraph on page 13, lines 5-20:

In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

Numerous examples of modified siNA duplexes that meet the claim limitations can be also found in Table I and the Figures of the '378 provisional application. Support for the instant claims is therefore found not only in the above captioned paragraphs of the '378 application, but in numerous motifs and exemplary sequences shown therein.

Provisional application 60/386,782, filed June 6, 2002, supports the instant claims as follows:

The limitation of claims 52 and 59, part (a) *"each strand is between 18 and 24 nucleotides in length"* finds support at page 22, lines 16-18:

In one embodiment of the present invention, each sequence of a siRNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length.

The limitations of claims 52 and 59, parts (b) *"the sense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a*

terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand", (c) *"the antisense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides"*, and and (d) *"10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 52) and "10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 59),* all find support on page 10, lines 3-16:

> *In one embodiment, the invention features a siRNA molecule, wherein the sense strand comprises one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages, and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides, and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the sense strand; and wherein the antisense strand comprises any of between 1 and 10, specifically about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages, and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides, and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 pyrimidine nucleotides of the sense and/or antisense siRNA stand are chemically modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3', 5', or both 3' and 5'-ends, being present in the same or different strand.*

Numerous examples of modified siNA duplexes that meet the claim limitations can be also found in Table I (see for example SEQ ID NOs: 319, 320, 322, 329, 332, 335, 338, 343, 344, 345, 346, 347, 348, 353, 355, 357, 359, 361, 363, 365, 366, 368, 370, and 371, amongst many others when used in combination with any of these sequences) and the Figures (see for example Figures 3 and 7) of the '782 provisional application. Support for the instant claims is therefore found not only in the above captioned paragraphs of the '782 application, but in numerous motifs and exemplary sequences shown therein.

Provisional application 60/358,580, filed February 20, 2002, supports the instant claims as follows:

The limitation of claims 52 and 59, part (a) *"each strand is between 18 and 24 nucleotides in length"* finds support at page 22, lines 12-14:

> *In one embodiment of the present invention, each sequence of a siRNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length.*

The limitations of claims 52 and 59, parts (b) *"the sense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand"*, (c) *"the antisense strand comprises one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides"*, and and (d) *"10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 52) and "10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides" (claim 59),* all find support in the paragraph spanning pages 9 and 10:

> *In one embodiment, the invention features a siRNA molecule, wherein the sense strand comprises one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages, and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides, and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the sense strand; and wherein the antisense strand comprises any of between 1 and 10, specifically about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages, and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides, and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 pyrimidine nucleotides of the sense and/or antisense siRNA stand are chemically modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3', 5', or both 3' and 5'-ends, being present in the same or different strand.*

Numerous examples of modified siNA duplexes that meet the claim limitations can be also found in Table I (see for example SEQ ID NOs: 323, 324, 326, 333, 336, 339, 342, 347,

348, 349, 350, 351, and 352, amongst many others when used in combination with any of these sequences) and the Figures (see for example Figures 3 and 7) of the '580 provisional application. Support for the instant claims is therefore found not only in the above captioned paragraphs of the '580 application, but in numerous motifs and exemplary sequences shown therein.

Claim Rejections – 35 U.S.C. 103(a)

The Office rejected claims 52-56 under 35 U.S.C. 103(a) as allegedly being obvious in view of Elbashir (EMBO J., 2001, 20(23):6877) in view of Nyce (WO 99/13886), Parrish (Molecular Cell, 2000, 6:1077-87), Matulic-Adamic (US 5,998,203), Bertrand (Biochemical & Biophysical Research Commun., 2002, 296:1000-1004); Braasch (Biochemistry, 2002, 41(14):4503-4510), and Olie (Biochimica et Biophysica Acta, 2002, 1576:101-109). Applicant respectfully traverses the rejection. Claim 53 has been canceled, thus rendering the rejection moot with respect to claim 53. Applicant respectfully traverses with respect to claims 52 and 54-64.

Applicant respectfully submits that the presently claimed invention cannot be obvious for at least four reasons. First, Braasch, Bertrand, and Olie are not proper prior art references that could render the instant claims obvious because they were all published after the priority date to which the instant claims are entitled. Second, one of skill in the art would *not have had any reasonable expectation of success* in practicing the claimed invention at the time of the invention because the prior art either taught away from the claimed invention or indicated a high level of unpredictability that would have precluded any reasonable expectation of success. Third, it is impermissible hindsight to conclude that the present invention is obvious because it would have been "obvious to try" the combinations of known modifications using "routine optimization," especially since the prior art gave *"no direction as to which of many possible choices is likely to be successful"* and offered *"only general guidance as to the particular form of the claimed invention or how to achieve it." In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988). Finally, even if a *prima facie* finding of obviousness can be established, the *failure of others*, along with the *surprising results* obtained in practicing the invention, serves to effectively rebut any such presumption of obviousness.

1. Priority

As explained above, Applicant respectfully submits that the instant claims are entitled to a priority date of February 20, 2002, on which the U.S. Provisional Application 60/358,580 was filed. Therefore, at least Braasch *et al.* (published on April 9, 2002), Bertrand *et al.* (published on August 21, 2002) and Olie *et al.* (published July 19, 2002) are not proper prior art references to render the instant claims obvious. As such, based on priority alone, Applicant respectfully submits that the instant claims are not *prima facie* obvious.

2. No reasonable expectation of success

In finding the claims obvious, the Office maintains that "one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes, as evidenced by Elbashir *et al.,* Nyce, Matulic-Adamic *et al.,* Parrish *et al.,* and Olie *et al.,* wherein each of the molecules face similar delivery challenges, and each of which can be improved with modifications, as evidenced by Braasch *et al.*" Office action, at page 13. The Office couples the alleged reasonable expectation of success with an alleged motivation for one skilled in the art to make and test siRNA duplexes with varied degrees of modifications, eventually leading to modified duplexes encompassed by the pending claims. Specifically, the Office states that because "Elbashir *et al.* is silent as to modification between 19% and 100%," one skilled in the art would be motivated to "modify more extensively than the 19% to optimize the activity/stability balance." Office action, at page 16. Applicant respectfully traverses.

Applicant maintains that Elbashir *et al.* teaches away from one of skill in the art making and testing siRNA duplexes that are more extensively modified than those shown in Figure 4 of the reference to maintain RNAi activity. Elbashir *et al.* describes siRNA duplexes having from 9.5% to 100% of the nucleotides modified by replacing the 2'-hydroxyl group of said nucleotides with either 2'-deoxy or 2'-O-methyl. Figure 4 shows that when the two, overhanging 3' nucleotides of each strand were modified (representing 9.5% of duplex nucleotides), RNAi activity was maintained. The same result was found when the two additional nucleotides adjacent to the 3' overhangs of each strand were modified (representing 19% of the duplex

nucleotides). However, when either one strand of the duplex was modified (representing 50% of the duplex nucleotides) or both strands of the duplex were modified (representing 100% of the duplex nucleotides), RNAi activity was abolished. The authors summarize their findings in the Discussion section of the paper in a "user guide" to those skilled in the art for generating siRNA duplexes that are both effective at gene silencing and more palatable from a manufacturing cost perspective. The authors state on page 6885, with emphasis added, the following:

> *Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes.* ***More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.***

Clearly, the Applicant and the Office have a much different interpretation of the teaching of Elbashir *et al*, hinging on the meaning of the phrase "more extensive" in the passage recited above. Applicant maintains this is a very strong teaching away from producing more extensively modified duplexes than those shown to maintain RNAi activity, *i.e.*, greater than 8 nucleotide modifications (*i.e.*, greater than 19% of the duplex nucleotides). In the alternative, the Office concludes that Elbashir *et al.* "in fact motivate[s] the skilled artisan to modify more extensively than the 19% to optimize the activity/stability balance." Office action at page 16. Importantly, in reaching this position, the Office incorrectly characterizes Elbashir *et al.* as being "silent as to modification between 19% and 100%." Office action at page 15. This leads the Office to conclude that the warning against making "more extensive" modifications in the user guide merely encompasses fully modified duplexes (*i.e.*, 100% modification). However, contrary to the Office's conclusion, and as described above, Elbashir *et al.* also teaches duplexes containing 50% modified nucleotides that have substantially reduced RNAi activity.

Applicant argues that the Office is basing its position on impermissible hindsight reasoning, taking into account the teachings of the Applicant's own disclosure. Applicant submits that one skilled in the art, at the time the invention was filed, would have first read the Elbashir reference as a whole and then concluded that said reference deeply discourages testing duplexes that are more extensively modified than those shown to maintain RNAi activity. Said

artisan would have first analyzed the data presented in Figure 4 of the publication, showing siRNA duplexes with 9.5% and 19% modified nucleotides with RNAi activity comparable to unmodified controls, and duplexes with 50% and 100% modified nucleotides with "abolished RNAi" activity. That same artisan would have then considered the authors' conclusions within *'The siRNA user guide,'* clearly indicating that more extensive modification beyond the 3'-terminal regions of one or both strands reduces activity by likely interfering with the ability of the duplex to associate with proteins required for activity. With this knowledge, and especially when considering the dramatic impact that even 50% of modified nucleotides had on RNAi activity of the Elbashir duplexes, Applicant argues that the skilled artisan would never have been motivated to tease out exactly what percentage modified nucleotides, *e.g.*, between 19% and 50%, would retain the RNAi activity of the control. Furthermore, Applicant submits that the skilled artisan, after reviewing Elbashir *et al.*, would certainly not have any reasonable expectation of successfully making and using siRNA duplexes with more extensive modifications than those shown in said reference to effectively silence genes.

To further highlight this point, it is important to recognize just how different the duplexes tested by Elbashir *et al.* are to those currently claimed. The siNA duplexes currently claimed require the following: a sense strand with one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications; a terminal cap moiety at the 3', 5', or both 3' and 5' ends of the sense strand; an antisense strand with one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications; and, 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro pyrimidine modifications of the sense strand and antisense strand (claim 52) or 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro pyrimidine modifications of the sense strand or antisense strand (claim 59). The modifications of the claimed duplexes are clearly well beyond modification of the up to four, 3'-terminal nucleotides of both strands described in Elbshair *et al.*, and thus embody the "more extensive" modification that Elbashir specifically warns against in the *'The siRNA user guide.'*

The Federal Circuit held in *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.,* 567 F.3d 1314 (Fed. Cir. 2009) that a prior art reference teaches away from the claimed invention if a

combination would not have worked *for the intended purpose* of the claimed invention, specifically where "the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." 567 F. 3d. at, 1325-28. Furthermore, where insight of an inventor is contrary to the understanding and expectations of the art, a structure effectuating it would not have been obvious. *Schenck v. Nortron Corp.*, 713 F.2d 283, 785 (Fed. Cir. 1983). The Supreme Court emphasized the key importance of a teaching away reference, stating that, "[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR Int'l Co.* 127 S. Ct. 1727, 1740 (2007 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). Clearly, proceeding when there is a teaching away supports nonobviousness, not motivation. See also, MPEP §2145 ("proceeding contrary to accepted wisdom is evidence of nonobviousness").

The Parrish reference, published prior to the Elbashir reference and sharing common authors, does not remedy the shortcomings of Elbashir, let alone the strong teaching away provided therein. In fact, the Parrish reference provides additional teachings away. The Office continues to mischaracterize the teachings of Parrish, stating that "Applicant's assertion regarding Parrish teaching away from 2'-deoxy modifications is completely unfounded given that Parrish specifically teaches 2'-deoxy incorporation with strong RNA interference activity." Office action, at page 16. Applicant respectfully questions the Office's reading of Parrish. Specifically, Parrish teaches that 2'-deoxy modification, *i.e.*, modification of cytidine to deoxycytidine or uracil to thymidine, on either the sense or the antisense strand produced a *substantial decrease in interference activity*. Parrish, at page 1081, right column (emphasis added):

> *A second position at which modifications were tested was the 2' position of the nucleotide sugar.* ***Modification of cytidine to deoxycytidine (or uracil to thymidine) on either the sense or the antisense strand of the trigger was sufficient to produce a substantial decrease in interference activity (Figure 5B).***

Parrish also teaches away from applying more than one phosphorothioate modification to different nucleotide bases because incorporation of more than one phosphorothioate base

modification *greatly reduced RNAi activity*, while incorporating more than two phosphorothioate base modifications *abolished RNAi activity*. Parrish, at page 1084, (emphasis added):

> *RNAs with two [phosphorothioate] modified bases also had* ***substantial decreases*** *in effectiveness as RNAi triggers (data not shown); modification of more than two residues* ***greatly destabilized*** *the RNAs in vitro and* ***we were not able to assay interference activities.***"

There is nothing in Nyce, Matulic-Adamic, Bertrand, Braasch, or Olie to remedy the shortcomings or teaching away that is evident in both Elbashir and Parrish, which are the only references that speak to modified double stranded nucleic acids that mediate RNA interference. In fact, the Bertrand reference, which was published August 30, 2002 and is thus post-filing art, reinforces Applicant's position that one would be neither motivated nor have any reasonable expectation of success in "more extensive" modification of siRNA.

The Bertrand reference, which is the only other cited reference to even mention siRNA, provides a comparison of modified antisense and native siRNA with respect to inhibition of green fluorescent protein both *in vitro* and *in vivo*. As such, the Office proposes that, after reading the Bertrand reference, one of skill in the art would have been motivated to incorporate the same modifications used in their antisense oligonucleotides into siRNA duplexes "for the same purpose of enhancing uptake of the molecule," especially considering the showing by Bertrand *et al.* that "siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides." Office action, at page 9. However, the Office fails to truly appreciate that Bertrand *et al.* compared *modified* antisense to *unmodified* siRNA, finding that siRNAs lacking any stabilizing modifications appear to be quantitatively more efficient (*i.e.*, with a longer lasting effect) than modified antisense oligonucleotides. One of skill in the art, after reading both Elbashir *et al.*, teaching that modifications greater than 8 nucleotide (*i.e.*, greater than 19% of the duplex nucleotides) reduce siRNA activity, and Bertrand *et al.*, showing that unmodified siRNA is superior to modified antisense in inhibiting gene expression, would certainly not be motivated to modify siRNA more extensively than the Elbashir duplexes shown to maintain RNAi activity. Why would one of skill in the art venture to modify siRNA duplexes when unmodified siRNA was shown by Bertrand *et al.* to be better in inhibiting gene

expression than modified antisense, especially when considering that more extensive modifications of the siRNA may negatively impact RNAi activity?

In conclusion, Applicant submits that the Office's conclusions are a result of impermissible hindsight influenced by the Applicant's own teachings. Therefore, the proposition that one of skill in the art, armed with the teachings of Elbashir, Parrish, Matulic-Adamic, Bertrand, Braasch, and Olie, would be both motivated and have a reasonable expectation of success in arriving at the claimed invention simply cannot stand.

3. "Obvious to try" analysis fails to find obviousness

The Office asserts that "incorporating the modifications at various percentages in the double stranded nucleic acid molecules of Elbashir *et al.* is considered within the realm of routine optimization." Office action, at pages 13-14. In doing so, the Office appears to rely on hindsight in putting forth the proposition that sooner or later, one of skill in the art would arrive at the instant invention by testing various combinations of modifications, i.e. "it remains within the technical grasp of the skilled artisan and within the realm of routine optimization to combine the known modifications of the prior art into various combinations and to expect to arrive at molecules with some degree of inhibitory activity within the instant broad genus of molecules having varying degrees of modification with various possible combinations of modifications." Office action, at pages 14-15.

The Office is essentially arguing that the present invention would be "obvious to try" using known modifications and routine experimentation, and is therefore *prima facie* obvious. Applicant respectfully traverses. The Federal Circuit has clarified the standard for a finding of obviousness based on "obvious to try" in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). While acknowledging that, as stated by the U.S. Supreme Court in *KSR International Co. v Teleflex Inc.,* a skilled artisan, when motivated by an unmet need, can look to combine elements within the scope of the prior art, it would be improper to hold a claim obvious when:

> *what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result; where the prior art gave either no indication of which parameters were*

critical or no direction as to which of many possible choices is likely to be successful

or

what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

To hold a claim obvious under these situations would be, according to the Federal Circuit, "succumb[ing] to hindsight claims of obviousness" and erroneous. *Id.* Reaffirming its prior holdings in *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit explained that in order for an "obvious to try" inquiry to serve as the basis for obviousness, some direction in the prior art that would provide a reasonable expectation of success is still required. *See, O'Farrell,* at 903-04. Not only did the references cited herein provide no guidance as to what individual modifications when used "more extensively" can result in siRNA molecules that are both active and stable, they in fact indicate that more extensive incorporation of these modifications into siRNA is detrimental, or at least highly unpredictable. The prior art references therefore provide no guidance or any level of predictability that would allow one of skill in the art to have any reasonable expectation of success using *the combination of features* as presently claimed. Therefore, even an "obvious to try" inquiry fails to result in a finding of obviousness as one of skill in the art would simply have ***no reasonable expectation of success*** in practicing the instantly claimed invention.

A reading of the cited prior art reveals a vast number of possible modifications that were available to one of skill in the art at the time of the instant invention. The Office, in hindsight, attempts to oversimplify the criteria as being limited to only two choices, i.e. modification of purine vs. pyrimidine nucleotides in stating that "the only positions that are specified are purines vs pyrimidines, of which there are only two choices for the skilled artisan to incorporate modifications at." Office action, at page 15. However, the claims require specific selections from at least *4 different criteria*: (1) the number of modifications, i.e. 10 or more; (2) the types of modifications, i.e. 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, universal base, or phosphorothioate; (3) the positions of certain modifications, i.e. CAPs at the 3', 5', or both 3' and

5'-ends of the sense strand; and (4) the type of nucleotide that is modified irrespective of its position within the duplex, i.e. pyrimidine nucleotides. Therefore, the present invention could not have possibly arisen from routine optimization.

Even if one takes the position that routine testing with known modifications and known assays would ***eventually*** lead one of skill in the art to the presently claimed invention, this would be insufficient to establish a *prima facie* case of obviousness for at least two reasons. First, the references cited by the Office fail to give any indication of which parameters were critical to success, and in many instances taught away from the claimed modifications. Second, at the time of the present invention, RNAi was a new technology and the experiences of the antisense/ribozyme arts at most gave general guidance as to types of modifications one could apply to a short dsRNA molecule, providing merely a large selection of possibilities to choose from. These known modifications were individually demonstrated by those who first studied short dsRNA in the field to be sometimes feasible with limited application, but more often than not incompatible with RNAi activity. That unpredictability grows only larger if the known modifications were applied more extensively, and in combination, as is presently claimed. Thus, although numerous types of modifications were known in the art, this was not a case of testing a finite number of identified, predictable solutions. ***"In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness."*** *Kubin,* at 1359.

Therefore, this is not an instance where the prior art contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, ***and evidence suggesting that it would be successful.*** Rather, it is an instance where the prior art provides no direction as to which of many possible choices is likely to be successful and only general guidance as to the particular form of the claimed invention or how to achieve it. Most importantly (as addressed previously), the prior art, by teaching away from more extensive modification, evidenced such a high level of unpredictability to preclude any reasonable expectation of success in practicing the claimed invention, which calls for (1) more extensive modification, i.e. 10 or more positions modified; (2) positional modification, i.e.

CAP modification of the 3', 5' or both 3' and 5' ends of the sense strand; (3) differential modification, i.e. modification of pyrimidines; and (4) particular modifications that were taught to abolish activity when used "more extensively", i.e. 2'-deoxy and 2'-O-methyl. Applicant's arguments do not rest on an absolute predictability of success, but rather point to a fundamental lacking of even a reasonable expectation of success. Any finding of obviousness under the "obvious to try" standard is therefore improper under the jurisprudence of *Kubin* and *O'Farrell*.

4. Secondary indicia preclude any finding of obviousness

Applicant maintains that no *prima facie* finding of obviousness can stand in view of the lack of motivation or any reasonable expectation of success that is evident from a plain reading of the cited art, and that even an "obvious to try" analysis fails because of the lack of guidance and/or predictability offered by the prior art. However, even if a *prima facie* showing of obviousness could be established, such a finding is effectively rebutted due to secondary considerations. It well established that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness". *Stratoflex, Inc. v. Aeroquip Corp*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Secondary considerations include the failure of others and unexpected results. MPEP 716.01(a). Specifically, (1) the failure of others, coupled with (2) the surprising results obtained using the instant invention, are a clear and irrefutable demonstration of non-obviousness with respect to the presently claimed invention.

The instant invention provides double stranded nucleic acid molecules that are both highly serum stable and potent in mediating RNA interference, both *in vitro* and *in vivo*. The closest prior art is the Elbashir reference cited herein. The authors of Elbashir, armed with all of the knowledge proffered by the prior art with respect to chemical modification of nucleic acids (including the Parrish, Matulic-Adamic, and Nyce teachings), who conducted extensive characterization and analysis of double stranded nucleic acid molecules with respect to optimized activity, and who published *'The siRNA user guide'* with respect to their findings; attempted to stabilize double stranded nucleic acid molecules, but *failed* in providing molecules that are both stable and active (see discussion below with respect to **Figure 3** of the instant

application). In fact, Elbashir taught that double stranded nucleic acid molecules that were "more extensively" modified beyond 2'-deoxy modification of the 3'-terminal nucleotide positions "reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." Elbashir, at page 6885, under *'The siRNA user guide.'* As such, Elbashir failed to arrive at a chemically modified double stranded nucleic acid molecule that is both serum stable and has retained (let alone improved or potent) activity.

The instant invention is a departure from the teachings of Elbashir's *'The siRNA user guide'* and provides double stranded nucleic acid molecules having features that impart a high level of serum stability yet maintain significant, or even improved, RNAi activity compared to those of the prior art (see **Figures 3, 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87** and **Table I and IV** of the instant application, specific examples of which are described in greater detail below). These features are presently claimed. Specifically, Claims 52 and 59 require that the sense strand have one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications and a terminal cap moiety at the 3', 5' or both 3' and 5'-ends of the sense strand. Claims 52 and 59 also require that the antisense strand have one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications. In addition, Claim 52 requires modification of 10 or more pyrimidine nucleotides of the sense and antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro modifications. Claim 59 requires modification of 10 or more pyrimidine nucleotides of the sense or antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro modifications. The dependent claims provide for additional modifications as well, including 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate modifications of the sense strand (Claims 54 and 60), and 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate modifications of the antisense strand (Claims 55 and 61). In this regard, even the minimal requirements of claims 52 and 59 differ substantially from the teachings of Elbashir in terms of structure, and result in double stranded nucleic acid molecules with surprising and unexpected properties (as described below).

The Office asserts that "the instant claims are not directed to any specific pattern that is stationary from target sequence to target sequence that has shown some sort of unexpected

property." Office Action, at page 17. Applicant respectfully disagrees with this characterization of the invention and maintains that the invention, when properly understood, is directed to a specific and uniform "pattern" of features that can be applied to any double stranded nucleic acid sequence as described in the specification, and which provides unexpected results. For example, application of the features of claims 52 or 59 to any duplex sequence will result in a specific structure with well defined features that include: (1) the length of each strand; (2) one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications and caps at the 3', 5' or both 3' and 5'-ends of the sense strand; (3) one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications of the antisense strand; and (4) 10 or more pyrimidine nucleotides of the sense and antisense strand modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides (claim 52) or 10 or more pyrimidine nucleotides of the sense or antisense strand modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. Application of these features results in short interfering nucleic acid molecules having high serum stability coupled with a high level of activity/potency. These surprising and unexpected properties are described below.

Application of the claimed features to a double stranded nucleic acid sequence of interest provides surprising and unexpected results. These unexpected results are clearly taught by the application as filed. Examiners must consider comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims. *In re Margolis*, 785 F.2d 1029, 228 USPQ 940 (Fed. Cir. 1986). For example, inspection of **Figure 3** of the instant application shows a direct comparison of the state of the art at the time of the invention (modified Elbashir duplex, Figure 4 on page 6882 of Elbashir *et al.*) to duplexes of the instant invention in terms of nuclease stability. The Elbashir duplex, having 3'-terminal 2'-deoxy modifications (SEQ ID NOs: 394 and 395, also shown above), when tested in human serum, has a half life (T ½) of *15 seconds*. The duplexes of the instant invention however, all having 3' and 5'-caps combined with 10 or more enumerated pyrimidine modifications, all show dramatically improved nuclease stability: T ½ of *138 minutes* for SEQ ID NOs: 396 and 397; T ½ of *3.7 days* for SEQ ID NOs: 396 and 398; T ½ of

72 minutes for SEQ ID NOs: 396 and 399; T ½ of *40 days* for SEQ ID NOs: 396 and 400; and T ½ of *32 days* for SEQ ID NOs: 396 and 401.

Additionally, the RNAi activity of duplexes of the invention, all having sense strand caps combined with 10 or more of the enumerated pyrimidine modifications (2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro) of the sense strand and/or antisense strand, is surprisingly *comparable to or even improved* when compared to a control duplex of the prior art. See for example **Figure 14**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 6" (see Table IV) sense strand (sequence 30222, SEQ ID NO: 373) consisting of 3' and 5'-terminal caps with 2'-O-methyl and 2'-deoxy pyrimidine modifications and various "Stab 5" (Table IV) antisense strands, all having 2'-deoxy-2'-fluoro and 2'-deoxy pyrimidine modifications (sequence 30546, SEQ ID NO: 386; sequence 30224, SEQ ID NO: 374; sequence 30551, SEQ ID NO: 387; sequence 30557, SEQ ID NO: 388, and sequence 30558, SEQ ID NO: 389). Also, see for example **Figure 15**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 4", "Stab 8" or "Stab 7" (Table IV) sense strand (sequence 30063, SEQ ID NO: 372; sequence 30434, SEQ ID NO: 384; and sequence 30435, SEQ ID NO: 385 respectively) all consisting of 3' and 5'-terminal caps with 2'-deoxy, 2'-deoxy-2'-fluoro or 2'-O-methyl pyrimidine modifications and a "Stab 8" (Table IV) antisense strand having 2'-deoxy-2'-fluoro pyrimidine and phosphorothioate modifications (sequence 30430, SEQ ID NO: 375). As shown in these figures, the activity of the serum stable double stranded nucleic acid molecules of the invention is an *unexpected finding* in view of the teachings of the closest prior art.

The unexpected results, contrary to the teaching of the prior art are also clearly exemplified in **Figures 28, 29, and 30**, in which the RNAi activity of various duplexes of the invention (Stab 4/5; Stab 7/8, and Stab 7/11 respectively, all having sense strands with 3' and 5'-terminal caps combined with 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with ribonucleotide (Stab 4, Table IV) or 2'-deoxy (Stab 7, Table IV) purines and antisense strands having 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with phosphorothioate modifications and with ribonucleotide (Stab 5, Table IV), 2'-O-methyl (Stab 8, Table IV) or 2'-

deoxy (Stab 11, Table IV) purines) are compared to an all RNA duplex control in inhibiting HBV gene expression in a dose response time course study (note, all sequences for the constructs in **Figures 28, 29, and 30** are all described in **Table I**). As shown in **Figures 28, 29, and 30**, the extensively and differentially modified duplexes of the invention all show comparable activity to the all RNA control at day 3, and *improved* activity at day 6 and day 9 time points.

As is clearly shown in **Figures 3, 14, 15, 28, 29, and 30** (amongst others), the double stranded nucleic acid molecules of the invention are significantly more stable than the double stranded nucleic acid molecules of the prior art, and surprisingly have retained or improved activity over the prior art molecules that allow these molecules to function as therapeutic modalities. The chemically modified duplexes of the instant invention are a significant and inventive advancement over the teachings of Elbashir *et al.*, who teach that "more extensive" modification is detrimental to RNAi activity and whose attempts to more extensively modify such molecules resulted in *abolished* activity. Thus, even if the Office were able to make a *prima facie* showing of obviousness (which is not the case), the failure of others combined with the surprising and unexpected results as taught by the application as filed and priority documents, unequivocally preclude any finding of obviousness.

Claim rejections – Double Patenting

The Office provisionally rejected claims 52-56 as allegedly being unpatentable on the ground of non-statutory obviousness-type double patenting over claims 1-20 of co-pending Application No. 12/170,290; claims 1-20 of co-pending Application No. 12/185,652; claims 1-20 of co-pending Application No. 12/204,572; claims 1-20 of co-pending Application No. 12/203,055; claims 1-20 of co-pending Application No. 12/200,736; claims 1-20 of co-pending Application No. 12/203,731; claims 1-20 of co-pending Application No. 12/204,612; claims 1-20 of co-pending Application No. 12/175,367; and claims 129-138 of co-pending Application No. 10/444,853. Office Action, at pages 18-23.

Applicant respectfully requests that the Office hold the provisional double-patenting rejections in abeyance until such time when they become the sole remaining rejections in the

instant application. Applicant then requests that these rejections be withdrawn in accordance with MPEP § 804 I.B., which states:

> *If the "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should then withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer.*

The instant application has the same effective priority date as its parent application, USSN 10/444,853, on which one of the provisional ODP rejections has been based.

Applicant will consider filing one or more terminal disclaimers, if appropriate, when the instant claims are held otherwise allowable.

Conclusion

In view of the foregoing, Applicant respectfully submits the pending claims are in condition for allowance but for the residual provisional double-patenting issues. If the Examiner believes a telephone conference would expedite prosecution of this application, she is urged to telephone the undersigned at the telephone number below.

Respectfully submitted,

Date: March 9, 2010

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